Armed Forces College of Medicine

AFCM

CNS fuels:

Ketone bodies metabolism and Ketosis

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INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be able to:

1. Mention different types of ketone bodies.
2. Illustrate ketogenesis and its regulation.
3. Illustrate ketone bodies utilization in peripheral tissues.
4. Mention the metabolic characters of ketosis.
5. Discuss the causes and mechanism of ketosis.
6. Interpret the different metabolic changes during ketosis.

Outline

- What are ketone bodies?
- Importance of ketone bodies as a source of energy
- Ketogenesis and Ketolysis
- Ketosis

Case scenario

A 35-year-old female became severely depressed after the sudden death of her husband. Two months later, she was brought to the emergency room

Case scenario

She appeared thin and pale. She had fruity odor of breath. Questioning revealed that she has not eaten for several days. Analysis of a blood sample revealed low blood glucose level (55 mg/dL) and elevated levels of

What are ketone bodies?

Ketone Bodies (KB)

Ketone Bodies: An Alternate Fuel For Cells

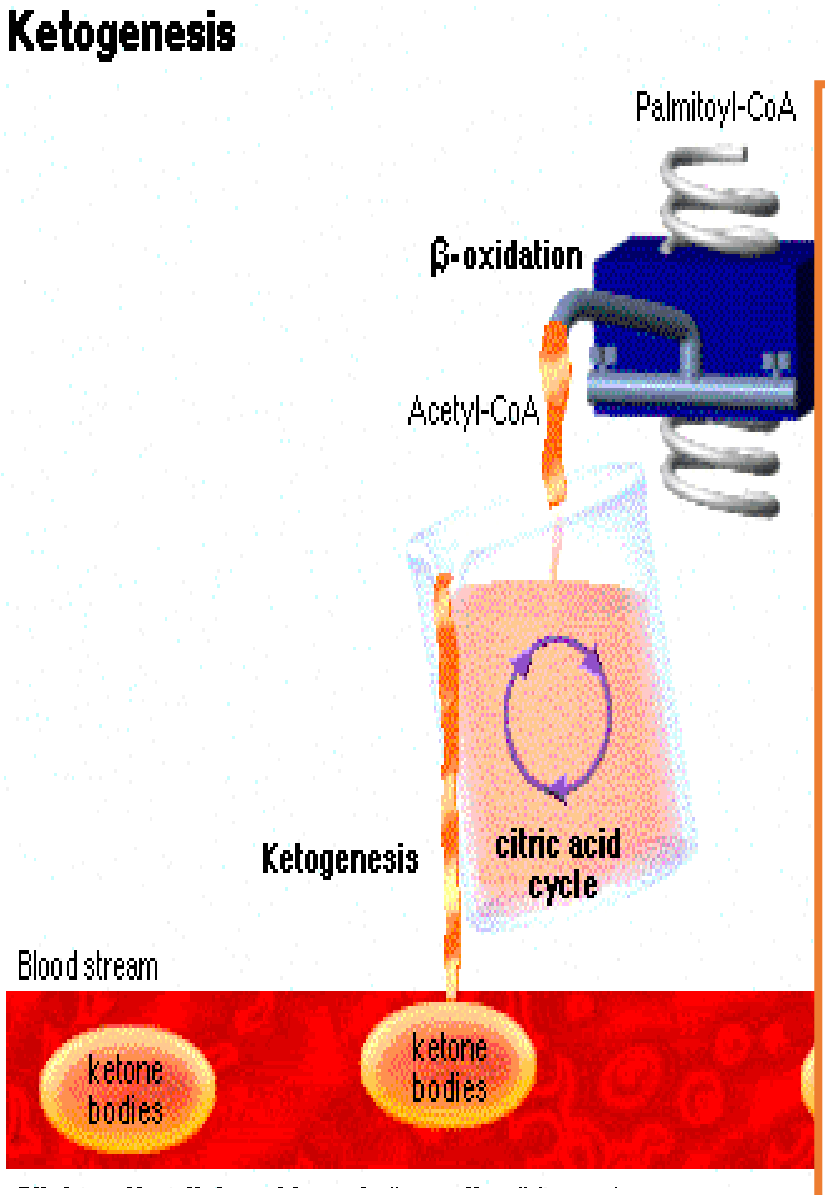
Li yl CoA derived from FA oxidation into ketone bodies.

- ✓ KB are organic acids: Acetoacetate & β-hydroxybutyrate (transported in the blood to the peripheral tissues) & Acetone (a non-metabolized product goes out with breath).
- ✓ The functional water-soluble KB (Acetoacetate & β-hydroxybutyrate) can be reconverted to acetyl CoA, which can be oxidized by the TCA cycle.

Terms

- **Ketogenesis:** The synthesis of Ketone bodies (KB), it occurs in the Liver.
- **Ketolysis:** The utilization process of KBs as fuels, it occurs in the extra hepatic tissues.
- **Ketosis:** Increase in the production of KB in the liver.
- **ketonemia:** High level of ketone bodies

Ketone Bodies (KB)



when **FA oxidation** is high in the liver, Acetyl CoA amount exceeds TCA capacity to oxidize it because there is no enough carbohydrates to provide oxaloacetate from the **pyruvate carboxylase** reaction (starvation, diabetes mellitus,

Ketone Bodies (KB)

- **The ketone bodies are *water soluble* and are *transported across the inner mitochondrial membrane as well as across the blood-brain barrier and cell membranes*.**

- **Thus they can be used as a fuel source by a variety of tissues including the CNS. They are preferred substrates for aerobic muscle and heart, thus sparing**

Ketone Bodies (KB)

Both

Ketogenesis

&

Ketolysis

Occur in ***Starvation***

Importance of ketone bodies as a source of energy

Why are KB important for peripheral tissues as a source of energy?

Because they are:

1) **Soluble** in water do not need lipoproteins or albumin as do the other lipids.

2) **Produced in the liver** when acetyl CoA exceeds the oxidative capacity of

Why are KB important for peripheral tissues as a source of energy?

Because they are:

3) **Used by extrahepatic tissues (skeletal and cardiac muscles and renal cortex). Even the brain can use ketone bodies to help meet its energy needs if the blood levels rise sufficiently.**

4) **Important during prolonged periods of fasting, thus ketone bodies spare glucose.**

Lecture Quiz

In Type I diabetes, the increased production of ketone bodies is primarily a result of which of the following?

A. a substantially increased rate of fatty acid oxidation by hepatocytes
B. an increase in the rate of the citric acid cycle
C. decreased cyclic adenosine monophosphate (cAMP) levels in adipocytes
D. elevated acetyl-CoA levels in skeletal

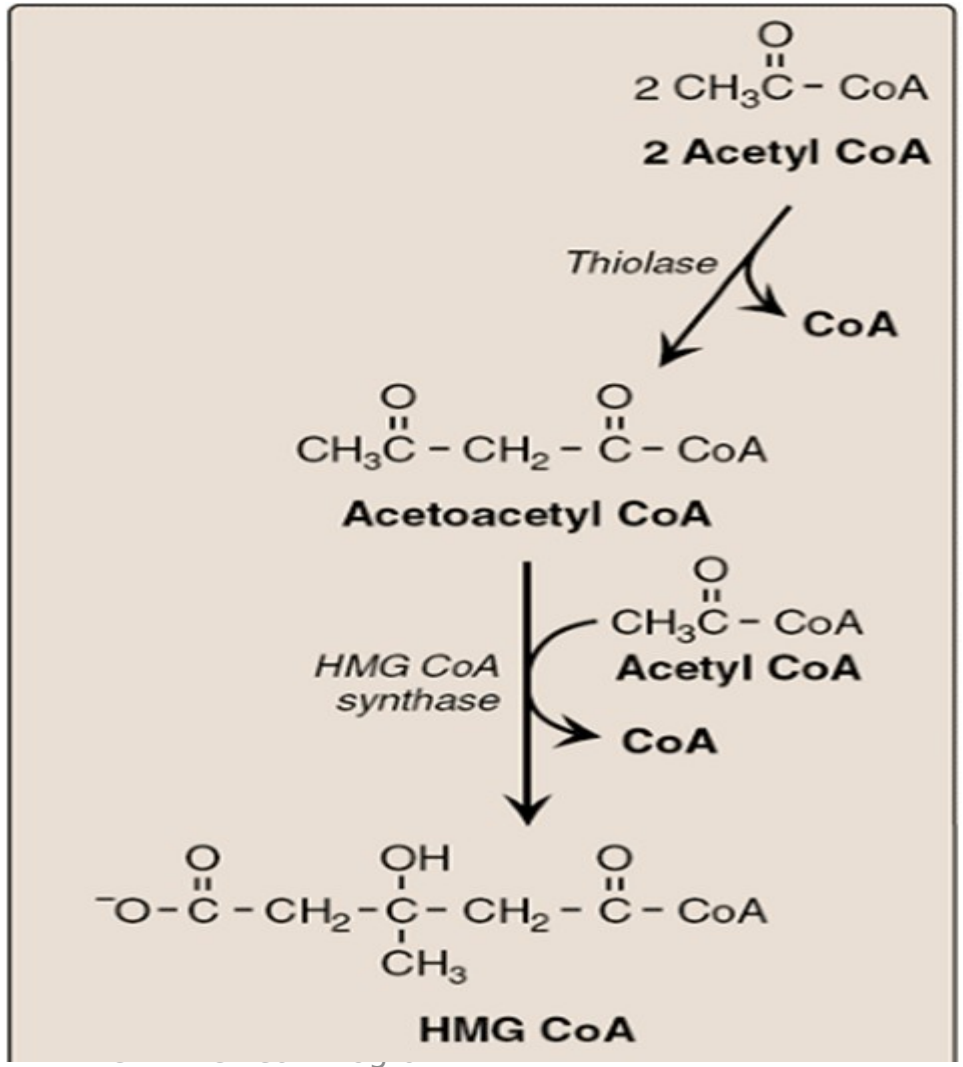
Ketogenesis and Ketolysis

A. Synthesis of ketone bodies by the liver: Ketogenesis

- ***At fasting state***, **the liver is full with FA mobilized from adipose tissue increasing hepatic acetyl CoA from FA degradation which inhibits *pyruvate dehydrogenase* and activates *pyruvate carboxylase*.**

- **The OA thus produced is used by the liver for gluconeogenesis rather than for TCA cycle. Therefore, acetyl CoA goes for KB**

A. Synthesis of ketone bodies by the liver: Ketogenesis



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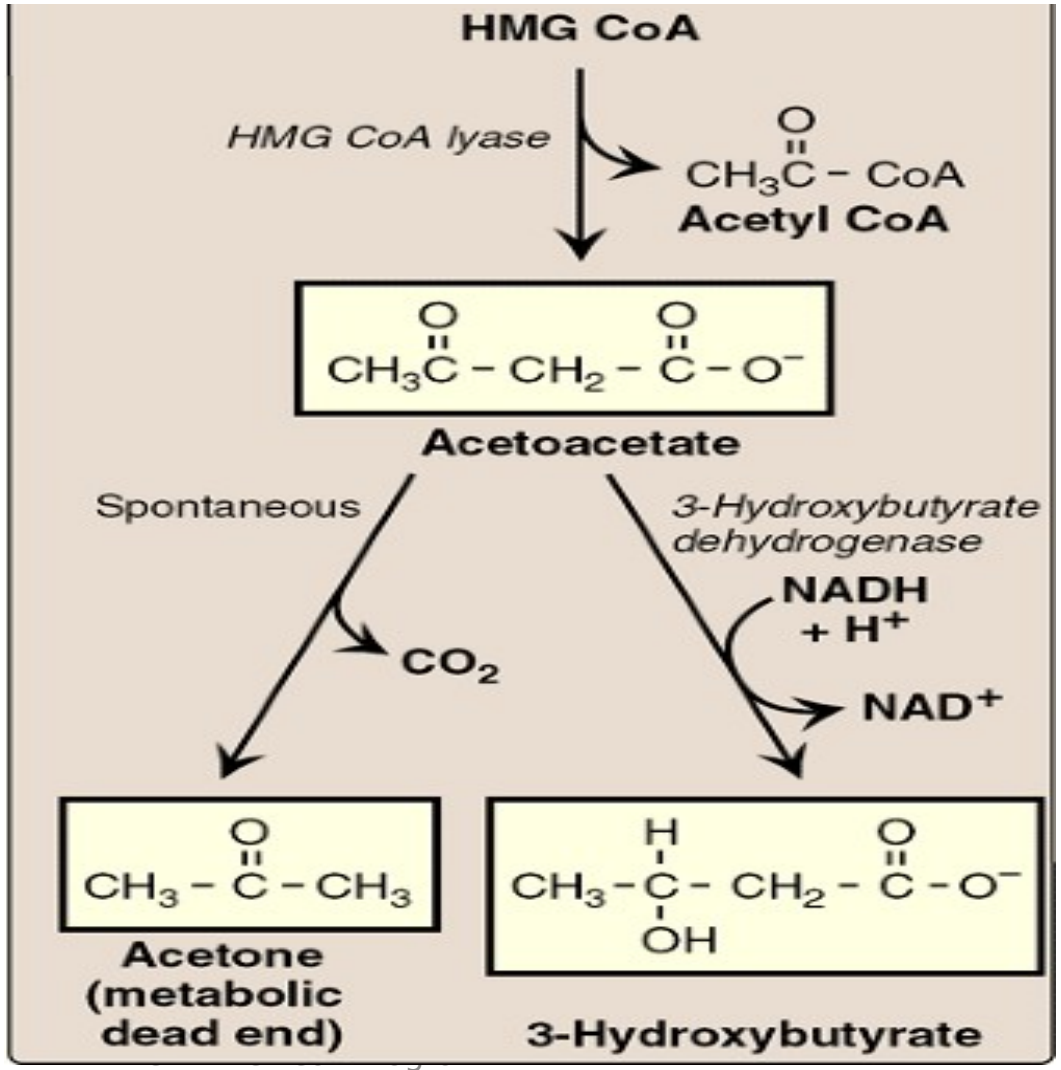
Synthesis of 3-hydroxy-3-methylglutaryl (HMG) CoA:

- **By *thiolase,* acetoacetyl CoA is formed. Mitochondrial *HMG CoA synthase* takes a 3rd acetyl CoA to produce HMG CoA (also a precursor of cholesterol).**
- ***HMG CoA synthase* is the rate-limiting step in**

A. Synthesis of ketone bodies by the liver: Ketogenesis



- **HMG CoA is cleaved to acetoacetate & acetyl CoA.**
- **Acetoacetate can be reduced to 3-hydroxy-butyrate with NADH or spontaneously be decarboxylate into acetone.**
- **Equilibrium between acetoacetate and 3-**

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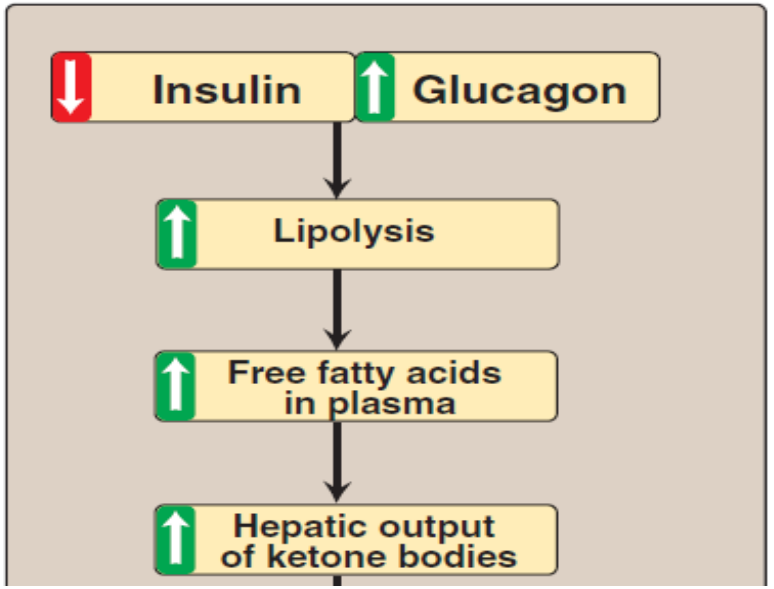
A. Synthesis of ketone bodies by the liver: Ketogenesis

REGULATION OF KETOGENESIS

Substrate level Regulation

Shortage of Carbohydrates leads to release of free FA from adipose tissue which directly affects the level of ketogenesis in the liver



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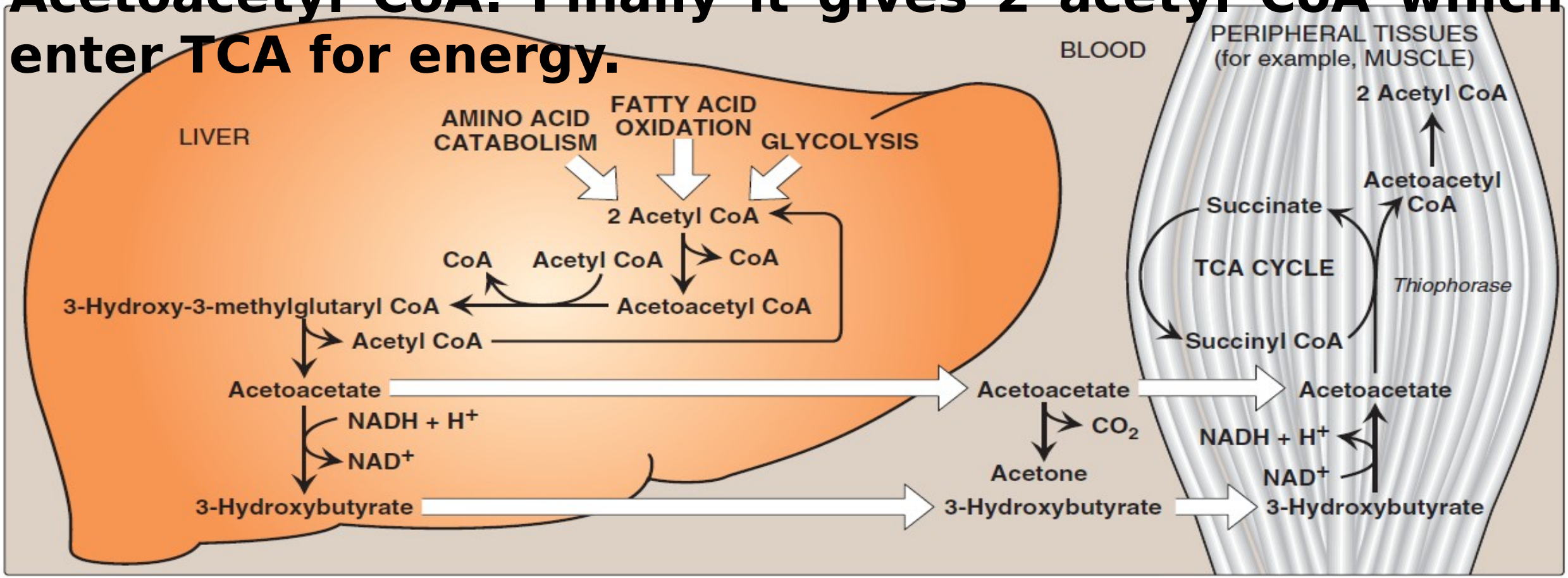
B. Use of ketone bodies by peripheral tissues: Ketolysis

- During **fasting**, **KBs** production by the **liver increases** as they are needed to provide **energy** to the **peripheral tissues**.
- **Although the liver** actively produces ketone bodies, it **lacks *thiophorase*** and, **therefore, is unable to use ketone**

B. Use of ketone bodies by peripheral tissues: Ketolysis

- **In contrast, extrahepatic tissues, including the brain but excluding cells lacking mitochondria (e.g. red blood cells), efficiently oxidize acetoacetate and 3-hydroxybutyrate in this manner.**

3-OH-butyrate oxidized to acetoacetate by *3-hydroxybutyrate dehydrogenase,* giving NADH. Acetoacetate+*succinyl CoA by acetoacetate succinyl CoA transferase (thiophorase)* (reversible) giving Acetoacetyl CoA. Finally it gives 2 acetyl CoA which enter TCA for energy.



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B. Use of ketone bodies by peripheral tissues: Ketolysis

Ketolysis is dependent on activity of citric acid cycle as succinyl-CoA needed for the thiophorase (acetyl coA transferase) reaction is supplied from citric acid cycle and acetyl-CoA

Lecture Quiz

Hepatocytes deliver ketone bodies to the circulation because they lack which of the following enzymes?

A. beta-hydroxybutyrate dehydrogenase
B. hydroxymethylglutaryl-CoA-lyase
C. hydroxymethylglutaryl-CoA-synthetase
D. succinyl-CoA-acetoacetate-CoA transferase
E. the form of the beta-ketothiolase

Ketosis

Ketone Bodies in Blood

- **The main ketone bodies of blood are *acetoacetate* and *3-hydroxybutyrate*, which are present at very low concentration. Normally ketone bodies in blood 0.5-3 mg/dL & in urine < 15 mg/day.**

- **Normally there is a balance between**

Ketone Bodies in Blood

- The rate of ketolysis is usually proportional to the concentration of ketone bodies in blood.

- As the rate of ketogenesis is ↑, the rate of ketolysis proportionally ↑ till reaching a maximum, after that, any ↑ in ketogenesis will produce ↑ in ketone

Ketosis

Ketogenesis >Ketolysis

It is a metabolic disorder characterized by a triad of:

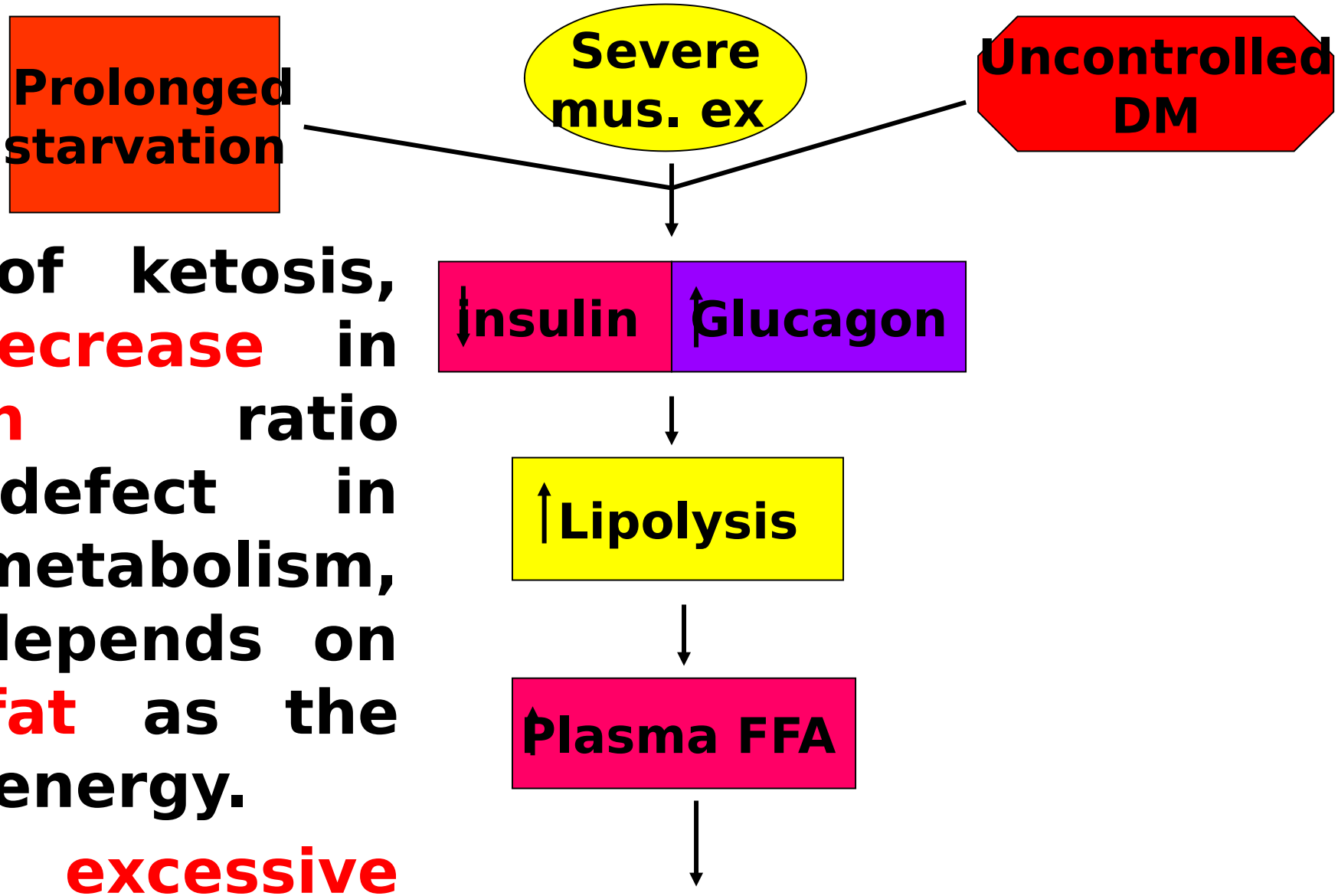
1. **Ketonemia (increase ketone bodies in blood).**
2. **Ketonuria (increase ketone bodies in urine).**

Ketosis

Causes of Ketosis:

1. Prolonged starvation.
2. low carbohydrates and high fat in diet.
3. Uncontrolled diabetes mellitus type I.
4. Prolonged and severe muscular exercise.
5. Prolonged administration of anti-insulin hormones.

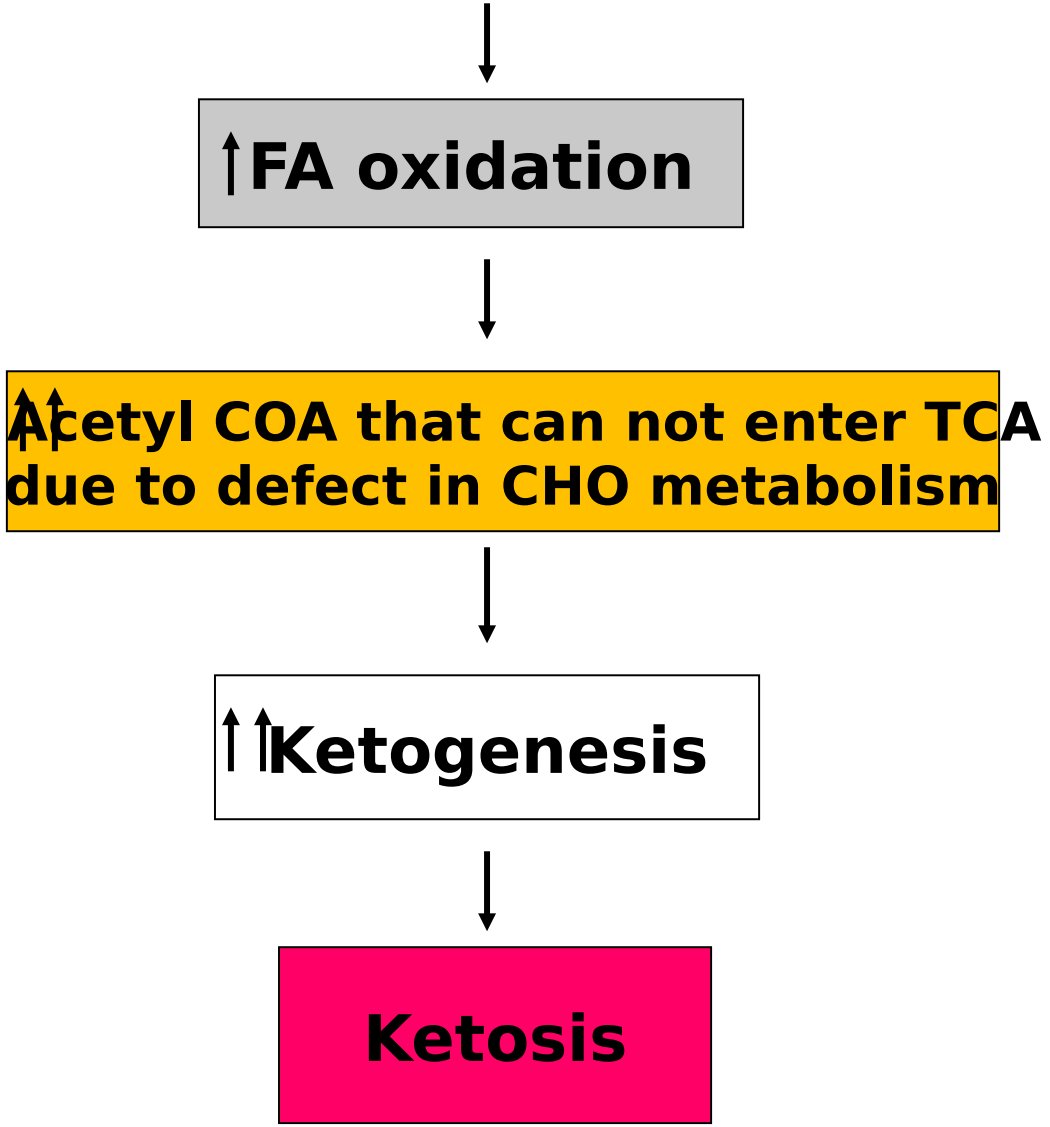
Mechanism of Ketosis:



- In all types of ketosis, there is a **decrease** in **insulin/glucagon** ratio causing a defect in carbohydrate metabolism, so the body depends on **oxidation of fat** as the main source of energy.
- So, there is **excessive lipolysis** in adipose tissue

Mechanism of Ketosis:

- The latter are oxidized to produce large amounts of acetyl COA that can not enter the citric acid cycle due to deficiency of oxaloacetate.
- Consequently, acetyl COA is diverted to the pathway of ketogenesis leading to excessive formation of



Ketogenic / Anti-ketogenic Factors

Ketogenic substances	Anti-ketogenic substances
Fatty acids	Carbohydrates
Ketogenic amino acids	Glucogenic amino acids
Anti-insulin hormones	Insulin
	Glycerol

Metabolic Changes during ketosis

There is a decrease in the insulin/anti-insulin ratio.

Organ	Metabolic changes
Adipose Tissues	↑ lipolysis that ↑ the release of FA and glycerol to blood
Liver	↑ FA uptake and oxidation, ↑ production of active acetate over the oxidative capacity of citric acid cycle due to: a)↑ ATP production from FA oxidation. b)Oxaloacetate is not available, as it is utilized by gluconeogenesis (stimulated by anti-insulin hormones and FA oxidation). **Accordingly, active acetate shifted to ketogenesis**.
Extrahepati	KBs Oxidation ↑ to a maximum, then any ↑ in

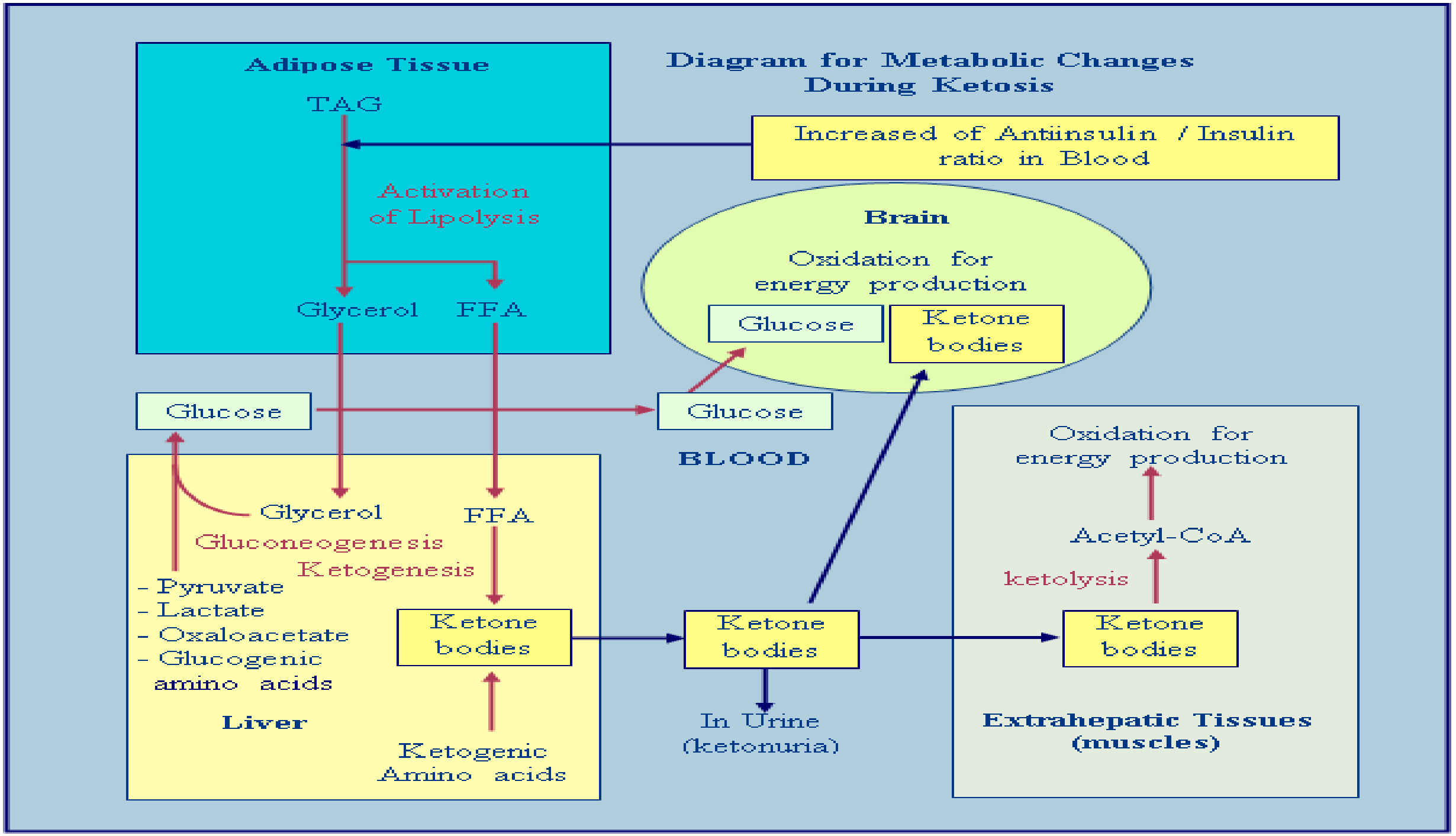
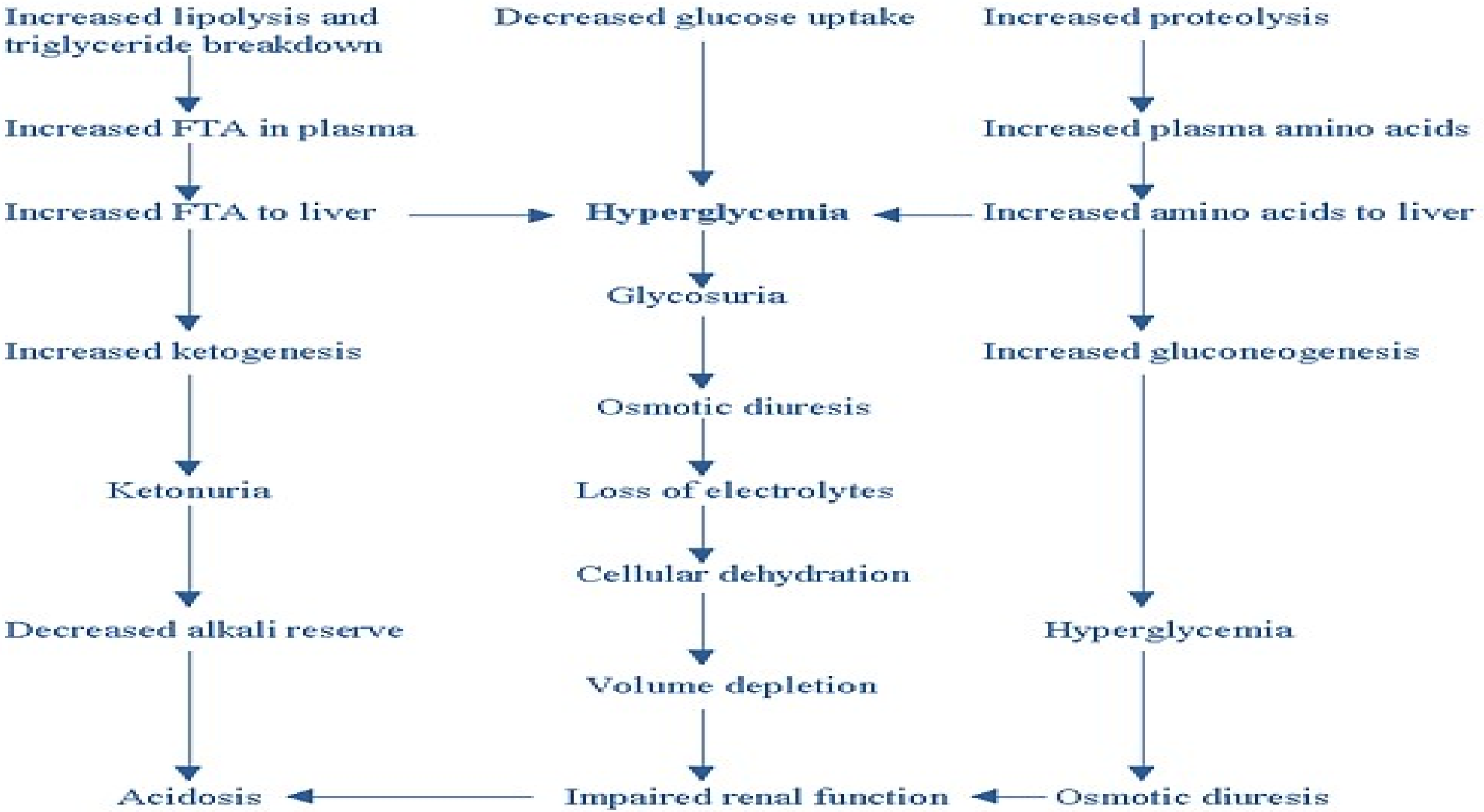


Diagram for Metabolic Changes During Ketosis
Adipose Tissue
TAG
Activation of Lipolysis
Glycerol
FFA
Increased of Antiinsulin / Insulin ratio in Blood
Brain
Oxidation for energy production
Glucose
Ketone bodies
Glucose
Glucose
BLOOD
Glycerol
FFA
Gluconeogenesis
Ketogenesis
- Pyruvate
- Lactate
- Oxaloacetate
- Glucogenic amino acids
Liver
Ketone bodies
Ketogenic Amino acids
Ketone bodies
In Urine (ketonuria)
Oxidation for energy production
Acetyl-CoA
ketolysis
Ketone bodies
Extrahepatic Tissues (muscles)

Consequences of ketosis

- The increased production and loss of 3-hydroxybutyrate and acetoacetate leads to loss of cations Na^+, K^+ and NH_4^+ in urine and decreased bicarbonate in the blood.
- Dehydration, due to excretion of glucose and ketone bodies in the urine.
- KB are strong acids (pKa=3.5). Therefore, the increased number of H+, circulating in a decreased volume of plasma lower the pH of blood and can cause severe acidosis (ketoacidosis). This acidity is dangerous because it impairs the ability of hemoglobin to bind oxygen.


Increased lipolysis and triglyceride breakdown
Decreased glucose uptake
Increased proteolysis
Increased FTA in plasma
Increased plasma amino acids
Increased FTA to liver
Hyperglycemia
Increased amino acids to liver
Glycosuria
Increased ketogenesis
Increased gluconeogenesis
Osmotic diuresis
Ketonuria
Loss of electrolytes
Cellular dehydration
Decreased alkali reserve
Hyperglycemia
Volume depletion
Acidosis
Impaired renal function
Osmotic diuresis

Treatment of ketoacidosis

- ✓ **Treatment is to give insulin & glucose.**

  Note: **when glucose & insulin are given intravenously, potassium is trapped within the cells.**

- ✓ **Administration of bicarbonate, and maintenance of electrolyte and fluid balance are very important aspects**

Lecture Quiz

Ketosis is the term used to describe which of the following?

A. The process of ketone bodies synthesis in the liver.
B. The utilization process of ketone bodies in the extra hepatic tissues.
C. Increase in the production of ketone bodies in the liver more than the rate of utilization.
D. The utilization process of ketone bodies in the liver.

Take Home Messages

- **The ketone bodies (acetoacetate, 3-hydroxybutyrate, and acetone) are formed in hepatic mitochondria when there is a high rate of fatty acid oxidation.**

- **The pathway of ketogenesis involves synthesis and breakdown of HMG-CoA by two key enzymes: HMG-CoA synthase and HMG-CoA lyase.**

Take Home Messages

- **Peripheral tissues possessing mitochondria can oxidize 3-hydroxybutyrate to acetoacetate, which can be reconverted to acetyl CoA, thus producing energy for the cell.**

- **The liver lacks the ability to degrade ketone bodies, and so synthesizes them specifically for the peripheral tissues.**

- **Ketoacidosis occurs when the rate of**

SUGGESTED TEXTBOOKS

1. "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R. Ferrier.

2. "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W. Rodwell.

Thank You